and mismatched the in vitro activity (EC_{50})" suggests that Jia and Wang may not have carefully read or understood our approach and the assumptions presented in the paper. We described HCQ dose regimen optimization in the Methods section as follows: "in a recent clinical trial, 500 mg of chloroquine phosphate given twice daily was shown to be effective on study day 5 (R_{LTEC}, day 5). This dosing regimen for chloroquine was used as the target for dose optimization for hydroxychloroquine." Although we calculated the R_{LTEC} for each compound (CQ and HCQ), we ultimately used relative potency between the 2 compounds to facilitate HCQ's dosing recommendations, rather than judging whether HCQ is effective or not. As compared to conventional methods that predict clinical efficacy based on in vitro and in vivo data of the same compound, our approach heavily relied on the emerging clinical antiviral effect by CQ (CQ was reported to be effective in 22 COVID-19 patients, as released on a clinical trial website and published later) [3–5]. Even for conventional methods, "mismatching" in vivo with in vitro data has been widely applied in drug development to understand the uncertainty of predicting in vivo efficacy/safety. The same concept has long been employed by industry and global regulators to predict clinical drug-drug interactions using different in vivo exposure measures for different interaction mechanisms. A recent analysis by Jansson-Löfmark et al [6] demonstrated a wide range of ratios of unbound trough concentration in plasma to in vitro potency for 164 marketed drugs across different indications. As such, we suspect that anyone can confidently claim a drug's in vivo efficacy based on in vitro data before the drug efficacy is determined clinically (otherwise, we would either skip or significantly shorten Phase II clinical trials in today's drug development).

We agree with Jia and Wang that "in vitro activity was significantly affected by experimental factors." Unfortunately, our group was 1 of the first reporting half maximal effective concentration (EC_{50}) of HCQ against SARS-CoV-2 [2]. Had we known other groups' findings at the time we did our analyses, we would have considered them in our analyses: for example, by conducting sensitivity analyses or using average data.

Finally, we would like to reiterate our response to an earlier letter to the editor: "although one can employ modeling and pharmacology concepts to predict the likelihood of clinical efficacy from in vitro data, given the inherent limitations of any modeling approach and assumptions being made, in vitro efficacy can only be ultimately confirmed through clinical trials. To this end, any modeling analysis has to fit for purpose" [7].

Notes

X. L. and Q. L. contributed equally to this work.

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Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Reinfection by a Phylogenetically Distinct Strain

To the Editor—To and colleagues reported the first documented case of an asymptomatic reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after 4.5 months [1]. As the patient experienced only mild symptoms during the first episode, the question remains whether a weak immune response after the first episode might explain the reinfection. It has been suggested that patients with an asymptomatic or mild SARS-CoV-2 infection have a weaker immune response because their antibody titers are significantly lower than in patients with pneumonia [2]. An estimated 20% do not seroconvert [3]. It also remains unclear whether patients can have a symptomatic reinfection. A recent Italian study reported no clinical reinfections within 3 months after hospital discharge [4]. We here report a symptomatic reinfection 93 days after a moderate SARS-CoV-2 infection.

In March 2020, a 51-year-old women presented to the general practitioner symptoms of headache, fever, myalgia,

Table 1. Reverse-Transcription Polymerase Chain Reaction (RT-PCR) and Full-length Genome-sequencing Results

	9 March 2020		10 June 2020
qPCR QuantStudio 7 (Applied Biosystems)[a]			
N-gene cycle threshold	25.6 (N1)		32.6 (N1)
	27.2 (N2)		33.2 (N2)
Full-length genomeGISAID accession number	EPI_ISL_522349		EPI_ISL_522350
SARS-CoV-2 lineage[b]	B.1.1		A
Observed mutations of strain B.1.1 versus strain A			
Position (bp)	**Base change**	**Gene**	**Mutation type**
3037	C/T	ORF1a	S
8782	C/T	ORF1a	S
11 654	C/T	ORF1a	NS (Phe to Leu)
14 408	T/C	ORF1b	S
17 427	T/G	ORF1b	S
23 403	G/A	Spike	NS (Gly to Asp)
23 873	A/G	Spike	NS (Thr to Ala)
24 726	C/T	Spike	NS (Ser to Leu)
28 881	A/G	Nucleocapsid	NS (Lys-Arg to Arg-Gly)
28 882	A/G	Nucleocapsid	
28 883	C/G	Nucleocapsid	

Abbreviations: Ct, cycle threshold; GISAID, Global Initiative on Sharing All Influenza Data; NS, nonsynonymous mutation; qPCR, quantitative polymerase chain reaction; S, synonymous mutation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]2019-nCoV CDC EUA kit.

[b]Nomenclature based on reference [5].

coughing, chest pain, and dyspnea. She also mentioned anosmia and a change in taste. She was not immunocompromised but took a daily dose of inhaled corticosteroids for asthma. A nasopharyngeal swab tested positive with SARS-CoV-2 polymerase chain reaction (PCR). Routine biochemistry and complete blood count did not show any abnormalities besides mildly elevated liver enzymes. Oxygen saturation by capillary oximeter was 94%. Hospitalization was not deemed necessary at the time, and the patient was asked to self-quarantine for 2 weeks. Because of persisting symptoms of tiredness, muscle pain, and dyspnoe, she stayed at home for 5 weeks before returning to work.

Three months after initial onset of symptoms, she experienced a relapse of symptoms with headache, cough, and fatigue. Rhinitis was also present. There was no travel history. The patient told the general practitioner that the symptoms felt similar to the first episode in March, although milder. The nasopharyngeal swab was again positive for SARS-CoV-2, suggesting a reinfection (Table 1). The symptoms resolved after 1 week. At that time, the patient tested positive for anti-SARS-CoV-2 nucleocapsid antibodies (Roche total immunoglobulin [Ig] signal/cutoff 134).

Full-length genome sequencing with ONT MinION revealed that the initial infection was caused by a lineage B.1.1 SARS-CoV-2 virus and the relapsing infection by a lineage A [5]. Eleven mutations were identified across the genome of the 2 strains (11/29 903 differences, 99.7% identity; Table 1). This difference is in line with other circulating strains in Belgium [6]. Documenting reinfection requires full-length genome sequencing or viral culture as PCR can remain positive for up to 104 days [7]. Usually asymptomatic and mild cases exhibit longer RNA shedding than severe cases [2].

The fact that a symptomatic reinfection with SARS-CoV-2 can occur already 3 months after the first infection is not unexpected. Symptomatic reinfections with human non-SARS coronaviruses are common and not atypical within 1 year after initial infection, despite the presence of antibodies. Reinfections with human non-SARS coronaviruses are, however, typically milder as was the case in our patient [8–10]. The fact that clinical reinfection can occur shortly after the first infection further underlines the fact that both healthcare workers and patients who had a prior SARS-CoV-2 infection are not always protected against reinfection.

Notes

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Call for Action: Racial Disparities in Clinical Research

To the Editor—We read with great interest the study by Olender et al [1]. To our knowledge, this is the first study showing significantly lower mortality in hospitalized patients with coronavirus disease 2019 (COVID-19) treated with remdesivir (RDV), compared with a similar cohort of patients receiving only the standard of care (SOC). The 2 groups were well-balanced and the statistical adjustments robust. However, 2 major findings merit further discussion.

On multivariate analysis, Black race was independently associated with 14-day mortality. Specifically, the odds of death for Black patients were more than 2-fold higher than for all other patients (odds ratio [OR], 2.4) [1], in agreement with our institutional experience [2]. Nevertheless, only 14% (42 of 298) of patients who received RDV were Black, in agreement with previously published data from the GS-US-540-5773 trial cohort [3]. In comparison, 29% (237 of 816) of those receiving only the SOC were Black, yielding an OR of 0.4 ($P < .001$). Therefore, compared with other races, Black patients with COVID-19 were more than twice as likely to die, but more than 2 times less likely to receive a potentially life-saving medication, through enrollment in a clinical trial.

This finding is in striking agreement with recently published data from a large registry of >2000 patients with history of cancer, in which Black race was associated with significantly lower likelihood of receiving RDV, with a similar effect size (OR, 0.56; $P = .05$) [4]. These discrepancies cannot be explained by differences in comorbidities and exclusion of patients because of impaired renal function, as in the study by Olender et al [1]. The exclusion criteria were also applied retroactively to the SOC cohort, whereas in the report by Rivera et al [4], there were no significant interactions between race and renal insufficiency.

Several reasons for this underrepresentation of racial and ethnic minorities in clinical trials have been recently highlighted [5–7]: poor health literacy and lack of trust in scientific methods on the part of the patients or their legal authorized representatives, implicit biases on the part of investigators, and limited access of vulnerable communities to institutions with resources to support complex/inclusive clinical trials. All of these factors can be exacerbated by the unique features of conducting clinical research amid a pandemic, such as infection control challenges during the consenting process, language barriers, misinformation with high-volume and poor-quality data [8], and the unprecedented pressure for high enrollment to rapidly produce meaningful results.

There is an urgent need for systemic platforms to analyze, discuss, and address racial and ethnic underrepresentation in COVID-19 clinical research. The National Institutes of Health already mandate adequate representation of all ethnic and racial groups in clinical studies, and other sponsors should promote standardized stratification and reporting [6]. It is critical that professional societies and scientific journals support the publication of real-world data in underserved patient populations and dedicated funding for projects addressing racial and ethnic disparities. Last, we propose the implementation and expansion of clinical research-focused educational modules for all research team members and healthcare workforce, aiming to promote awareness of individual and structural biases in everyday clinical practice.

Note

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